PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 October 1998 (21.10.98)	
International application No. PCT/US98/04258	**Applicant's or agent's file reference** 15280-3151PC
International filing date (day/month/year) 04 March 1998 (04.03.98)	**Priority date** (day/month/year) 05 March 1997 (05.03.97)
Applicant CHANDRASEKHARAPPA, Settara, C. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 October 1998 (02.10.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Dominique DELMAS

Telephone No.: (41-22) 338.83.38

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, C07K 14/47, G01N 33/574, C12Q 1/68, A61K 48/00, C12N 15/86, C07K 16/18, A01K 67/027

A1

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(71) Applicant *(for all designated States except US)*: THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Bethesda, MD 20892 (US).

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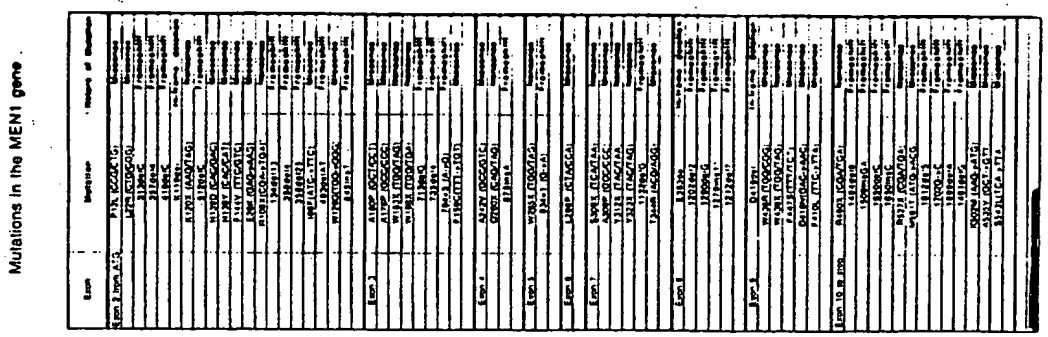
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: *MEN1*, THE GENE ASSOCIATED WITH MULTIPLE ENDOCRINE NEOPLASIA TYPE 1, MENIN POLYPEPTIDES, AND USES THEREOF



(57) Abstract

This invention relates to the discovery of a novel tumor suppressor gene which is associated with multiple endocrine neoplasia type 1. The gene has been designated *MEN1* and the gene product is menin. The absence of this protein and associated mutations in the corresponding gene have been identified in individuals suffering from multiple endocrine neoplasia type 1. The identification of this marker for multiple endocrine neoplasia type 1 has diagnostic uses as well as for gene therapy.

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PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
15280-3151PC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 98/ 04258	04/03/1998	05/03/1997

Applicant

THE GOVERNMENT OF THE UNITED STATES et al.

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [X] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [X] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 4
   - [ ] as suggested by the applicant.
   - [X] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/04258

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/47 G01N33/574 C12Q1/68 A61K48/00
C12N15/86 C07K16/18 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LARSSON C ET AL: "Multiple endocrine neoplasia type 1 gene maps to chromosome11 and is lost in insulinoma" NATURE, vol. 332, 3 March 1988, pages 85-87, XP002069543 ---	
P,X	CHANDRASEKHARAPPA S ET AL: "Positional cloning of the gene for multiple endocrine neoplasia-type 1" SCIENCE., vol. 276, 18 April 1997, pages 404-407, XP002069544 see the whole document ---	1-37

-/--

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 July 1998	16/07/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lonnoy, O

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	KEDRA D ET AL: "The germinal center kinase gene and a novel CDC25-like gene are located in the vicinity of the PYGM gene on 11q13" HUM. GENET., vol. 100, October 1997, pages 611-619, XP002069545 See "Note added in proof" ---	1-37
A	DATABASE EMEST13 E.M.B.L. DATABASE Accession Number: AA168218, 21 December 1996 MARRA M ET AL: "Mus musculus cDNA clone 608138" XP002070015 see abstract ---	
A	DATABASE EMEST13 E.M.B.L. DATABASE Accession Number: W89897, 7 July 1996 MARRA M ET AL: "Mus musculus cDNA clone 420339" XP002070016 see abstract ---	
A	DATABASE EMEST12 E.M.B.L. DATABASE Accession Number: AA000099, 20 July 1996 MARRA M ET AL: "Mus musculus cDNA clone 425424" XP002070017 see abstract -----	

PATENT COOPERATION TREATY

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19

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
15280-3151PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US98/04258	04/03/1998	05/03/1997
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant THE GOVERNMENT OF THE UNITED STATES... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/10/1998	05.05.99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Roscoe, R Telephone No. (+49-89) 2399 2554

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US98/04258

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-62 as originally filed

Claims, No.:

1-37 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11, 14-29, 32-35
	No:	Claims	12, 13, 30, 31, 36, 37
Inventive step (IS)	Yes:	Claims	1-11, 14-29, 32-35
	No:	Claims	12, 13, 30, 31, 36, 37
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Citations

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

The priority document pertaining to the present application was not available at the time of establishing this first written opinion. Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this assumption is incorrect, documents D2 and D3 cited in the search report could become relevant to the assessment of whether the present application satisfies the criteria set forth in Article 33(1) PCT.

2. Reasoned statement on Novelty, Inventive Step and Industrial Applicability (Section V)

D1 is the closest prior art. In said document, the MEN-1 locus is mapped to chromosome 11 in the vicinity of the human muscle phosphorylase gene. The exact position is not known, neither is anything about the nature of the gene itself.

D4 discloses a mouse-derived EST corresponding to a transcript running in the opposite direction to MEN-1 and covering parts of exons 7-10. D5 discloses a mouse-derived EST corresponding to most of exon 2 of MEN-1. D6 discloses a mouse-derived EST corresponding to part of exon 1 and most of exon 2. None of these ESTs have had a function attributed to them or have been identified as being linked to any condition.

2.1 Novelty (Art.33(2) PCT)

Claim 12 is not novel since a protein comprising Seq.ID No.2 can have any additional sequences which could comprise epitopes to which known proteins bind. Further, antibodies capable of binding menin may already exist. If applicant were to claim the raising of antibodies against menin he would automatically obtain protection for the products of this process. Similarly, in claim 13, both (i)

and (ii) allow for large undefined portions of protein - hence, claim 13 is also not novel.

A cell comprising a nucleic acid encoding a subsequence of unspecified size cannot be considered novel (claim 30)

Claim 31 is totally unacceptable since the length of the nucleotide that hybridizes is not disclosed. Undoubtedly, nucleotides which fall under the scope of the claim are known. (It is further noted that the scope of the claim extends far beyond anything that could be considered related to the problem solved by the applicant).

Novelty cannot be acknowledged for claims 36 and 37 until the menin polypeptide has been adequately technically defined.

2.2 **Inventive Step (Art.33(3) PCT)**

Claims 1-11, 14-29, 32-35 are inventive. The prior art stops far short of identifying the exact position of the MEN-1 gene. Further, no sequence information or functional information allowing one to narrow down the large number of candidate genes one would expect in the MEN-1 harbouring region was available. According to D3, many candidate genes have been screened for mutations and excluded as MEN-1 and the search has been proceeding for a number of years. Applicant was the first to select the correct gene for screening. Hence, the isolation of MEN-1 and its use to enable screening for patients harbouring mutations in this gene has to be considered inventive.

2.3 **Industrial Applicability (Art.33(4) PCT)**

Claims 1-37 appear to have industrial applicability

3. **Certain observations (Section VIII)**

3.1 **Clarity (Art.6 PCT)**

The term "menin" in claims 6, 14, 15, 19, 23-25, 27-30, 34 and 36 is an arbitrary

definition not known to the skilled person.

The term "stringent conditions" in claims 8 and 31 should be technically defined.

The meaning of "a nucleotide sequence essentially encoding" in claim 25 is absolutely unclear.

The 60% level of similarity in claim 9(b) is considered too broad - applicant should introduce the subject-matter of claim 10 into the claim. Even then, given the inability to functionally limit the claim the acceptability of the claim is questionable.

Claims 28 and 29 should presumably refer back to the kit of claim 27.